Chemistry of Heterocyclic Compounds, Vol. 41, No. 1, 2005

SYNTHESIS AND STRUCTURAL DETERMINATION OF 5-ARYLAMINO-1,3-DIMETHYLPYRAZOLES

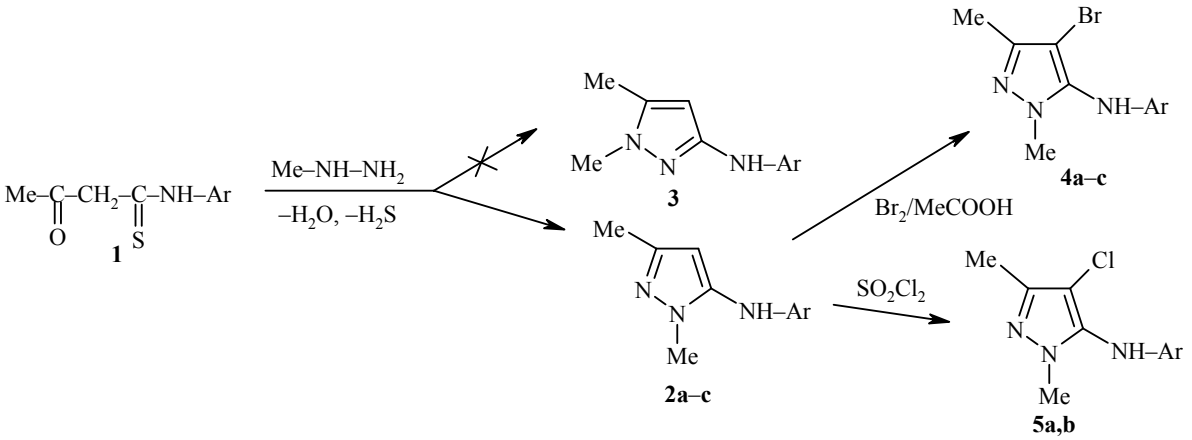
V. N. Britsun, I. M. Bazavova, V. N. Bodnar, A. N. Chernega, and M. O. Lozinskii

Treatment of 4-arylamino-4-thioxo-2-butanones with methylhydrazine in acetic acid gives 5-arylamino-1,3-dimethylpyrazoles which are readily halogenated in the 4 position. The thermal decomposition of 3-anilino-1,2,5-trimethyl-1H-pyrazolium chloride gives 1,3-dimethyl-5-phenylaminopyrazole and 1,5-dimethyl-3-phenylaminopyrazole in the approximate ratio of 1: 1.

Keywords: 4-arylamino-4-thioxo-2-butanone, 5-arylamino-1,3-dimethylpyrazoles, 1,5-dimethyl-3-phenylaminopyrazole, methylhydrazine.

Alkyl-5-arylaminopyrazoles are promising materials for pharmacological study [1], e.g. they can be used as antiallergic or antipyretic agents [2, 3]. More recently, the use of alkyl 5-arylaminopyrazoles as potential pesticides has been noted [4-6]. However, the simplest representatives of the 5-arylamino-1,3-dimethylpyrazoles and 5-arylamino-1,5-dimethylpyrazoles are virtually unknown in the literature with the exception of a study [7] in which the decomposition of a quaternary pyrazolium salt gave 1,3-dimethyl-5-phenylaminopyrazole.

It has previously been shown that 4-anilino-4-thioxo-2-butanones react with hydrazine to give 5-arylamino-3-methylpyrazoles [8, 9]. With the aim of preparing dialkylarylaminopyrazoles we now report the reaction of the 4-arylamino-4-thioxo-2-butanones **1a-c** with methylhydrazine in acetic acid. In this way both 5-arylamino-1,3-dimethylpyrazoles **2** and 3-arylamino-1,5-dimethylpyrazoles **3** may be formed.



1-5 **a** Ar = Ph, **b** Ar = *p*-ClC_6H_4; **2**, **4 c** Ar = *p*-BrC_6H_4

Institute of Organic Chemistry, Ukraine National Academy of Sciences, Kiev 02094, e-mail: iochkiev@ukrpack.net. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 120-126, January, 2005. Original article submitted December 30, 2002.

According to ^{1}H NMR spectroscopic data the reaction occurs in one way. The yields, melting points, and elemental analytical data for the compounds synthesized are given in Table 1 and the ^{1}H NMR spectroscopic data in Table 2. In the ^{1}H NMR spectra of the compounds prepared there are present signals for the NH groups (7.89-8.48), aromatic ring protons (6.75-7.41) and pyrazole ring protons (5.77-5.93 ppm). It should be noted that it is impossible to determine which of the isomers **2** or **3** is formed on the basis of the ^{1}H NMR data. According to the data in [8] the formation of compounds **2a-c** is more likely, however the melting point of the compound synthesized by us from 4-anilino-4-thioxo-2-butanone (148-150°C) is markedly different to the melting point reported in [7] for 1,3-dimethyl-5-phenylaminopyrazole (95°C). Hence an identification was made for the compound using X-ray structural analysis and it was found that it is 1,3-dimethyl-5-phenylaminopyrazole (**2a**) (see Fig. 1 and Table 3).

TABLE 1. Parameters for Compounds **2-5** and **7-9**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	N		
2a	$C_{11}H_{13}N_3$	70.71 / 70.56	6.88 / 7.00	22.10 / 22.44	148-150	86
2b	$C_{11}H_{12}ClN_3$	59.44 / 59.60	5.58 / 5.46	19.10 / 18.95	95-97	67
2c	$C_{11}H_{12}BrN_3$	49.78 / 49.64	4.81 / 4.54	15.71 / 15.79	120-122	73
3a	$C_{11}H_{13}N_3$	70.49 / 70.56	6.74 / 7.00	22.34 / 22.44	115-117	21
4a	$C_{11}H_{12}BrN_3$	49.48 / 49.64	4.69 / 4.54	15.60 / 15.79	105-107	70
4b	$C_{11}H_{11}BrClN_3$	43.61 / 43.95	3.39 / 3.69	13.74 / 13.98	115-117	62
4c	$C_{11}H_{11}Br_2N_3$	38.58 / 38.29	3.46 / 3.21	12.04 / 12.18	129-30	64
5a	$C_{11}H_{12}ClN_3$	59.83 / 59.60	5.23 / 5.46	18.71 / 18.95	108-110	58
5b	$C_{11}H_{11}Cl_2N_3$	51.44 / 51.58	4.40 / 4.33	16.68 / 16.41	93-95	65
7	$C_{12}H_{16}IN_3$	43.83 / 43.78	5.16 / 4.90	12.89 / 12.76	184-186	68
8	$C_{12}H_{15}N_3$	71.53 / 71.61	7.64 / 7.51	20.95 / 20.88	80-82	77
9	$C_{12}H_{16}ClN_3$	60.48 / 60.63	6.56 / 6.78	17.83 / 17.68	238-240	85

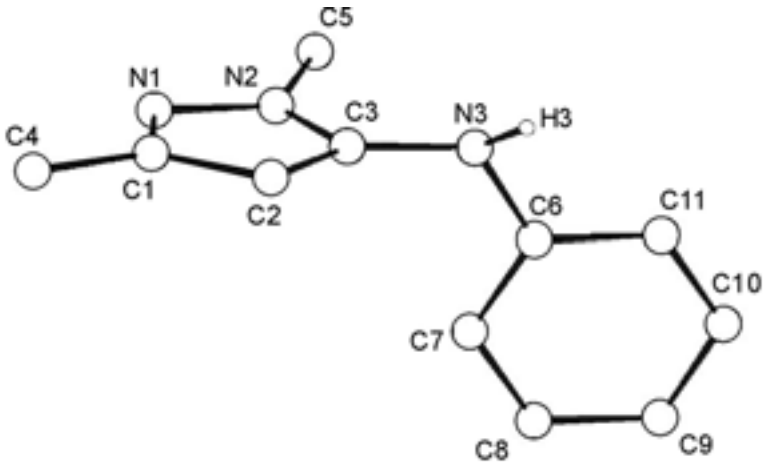


Fig. 1. Overall view of the molecule of **2a** with atom numbering.

TABLE 2. ^{1}H NMR Spectra of Compounds **2-5** and **7-9**

Com-pound	Chemical shifts (DMSO-d_6), δ, ppm (*J*, Hz)
2a	2.09 (3H, s, CH_3-3); 3.55 (3H, s, CH_3-1); 5.77 (1H, s, H-4 pyrazole); 6.75-7.18 (5H, m, C_6H_5); 7.88 (1H, s, NH)
2b	2.16 (3H, s, CH_3-3); 3.09 (3H, s, CH_3-1); 5.91 (1H, s, H-4 pyrazole); 6.95 (2H, d, *J* = 10.1, *o*-H_{Ar}); 7.28 (2H, d, *J* = 10.1, *m*-H_{Ar}); 8.45 (1H, s, NH)
2c	2.16 (3H, s, CH_3-3); 3.61 (3H, s, CH_3-1); 5.93 (1H, s, H-4 pyrazole); 6.87 (2H, d, *J* = 11.0, *o*-H_{Ar}); 7.41 (2H, d, *J* = 11.0, *m*-H_{Ar}); 8.48 (1H, s, NH)
3a	2.19 (3H, s, CH_3-5); 3.60 (3H, s, CH_3-1); 5.60 (1H, s, H-4 pyrazole); 6.67-7.28 (5H, m, C_6H_5); 8.26 (1H, s, NH)
4a	2.14 (3H, s, CH_3-3); 3.58 (3H, s, CH_3-1); 6.52-7.15 (5H, m, C_6H_5); 7.89 (1H, s, NH)
4b	2.12 (3H, s, CH_3-3); 3.56 (3H, s, CH_3-1); 6.56 (2H, d, *J* = 9.7, *o*-H_{Ar}); 7.20 (2H, d, *J* = 9.7, *m*-H_{Ar}); 8.09 (1H, s, NH)
4c	2.13 (3H, s, CH_3-3); 3.56 (3H, s, CH_3-1); 6.47 (2H, d, *J* = 9.2, *o*-H_{Ar}); 7.30 (2H, d, *J* = 9.2, *m*-H_{Ar}); 8.14 (1H, s, NH)
5a	2.13 (3H, s, CH_3-3); 3.56 (3H, s, CH_3-1); 6.54-7.13 (5H, m, C_6H_5); 7.95 (1H, s, NH)
5b	2.12 (3H, s, CH_3-3); 3.55 (3H, s, CH_3-1); 6.55 (2H, d, *J* = 10.1, *o*-H_{Ar}); 7.21 (2H, d, *J* = 10.1, *m*-H_{Ar}); 8.15 (1H, s, NH)
7	2.37 (3H, s, CH_3-5); 3.79 (3H, s, CH_3-1); 3.88 (3H, s, CH_3-2); 6.27 (1H, s, H-4 pyrazole); 7.08-7.39 (5H, m, C_6H_5); 9.23 (1H, s, NH)
8	2.08 (3H, s, CH_3-5); 3.20 (3H, s, CH_3-1); 3.25 (3H, s, CH_3-2); 5.52 (1H, s, H-4 pyrazole); 6.65-7.16 (5H, m, C_6H_5)
9	2.36 (3H, s, CH_3-5); 3.76 (3H, s, CH_3-1); 3.98 (3H, s, CH_3-2); 6.26 (1H, s, H-4 pyrazole); 7.10-7.38 (5H, m, C_6H_5); 10.05 (1H, s, NH)

The pyrazole ring $N_{(1)}N_{(2)}C_{(1)}C_{(2)}C_{(3)}$ is planar with a deviation of the atoms from the mean square plane not greater than 0.007 Å. The geometrical parameters of this ring point to a significant delocalization of the electron density and this is quite typical for analogous systems. The $C_{(3)}N_{(3)}C_{(6\text{-}11)}$ grouping is planar within the limits 0.020 Å and forms a dihedral angle of 76.2° with the five membered ring. The $N_{(2)}$ and $N_{(3)}$ atoms have, respectively, planar trigonal and slightly pyramidal configured bonds with overall valence angles of 359.9 and 350.8°. Via $N_{(3)}$–$H_{(3)}\cdots N_{(1)}$ intramolecular hydrogen bonds with mean values of $N_{(3)}\cdots N_{(1)}$ 3.00(6), $N_{(1)}\cdots H_{(3)}$ 2.10 (6), $N_{(3)}$–$H_{(3)}$ 0.90(6) Å, and $N_{(3)}H_{(3)}N_{(1)}$ 174(3)° the molecules of **2a** are combined in the crystal through infinite chains (Fig. 2).

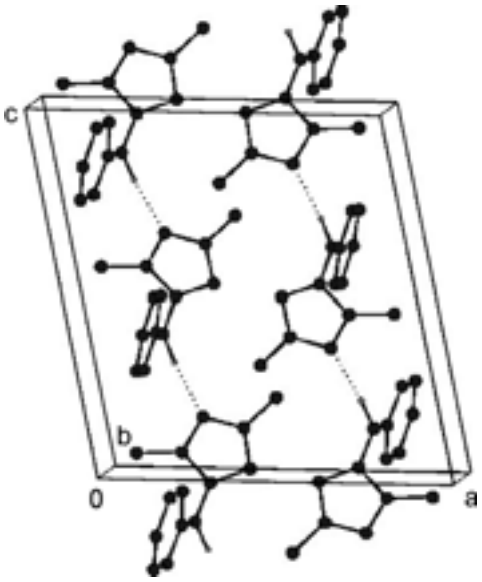


Fig. 2. Crystal packing of compound **2a** (intermolecular hydrogen bonds indicated by dotted lines).

TABLE 3. Interatomic Distances (*d*) and Valence Angles (ω) in the Molecule of Compound **2a**

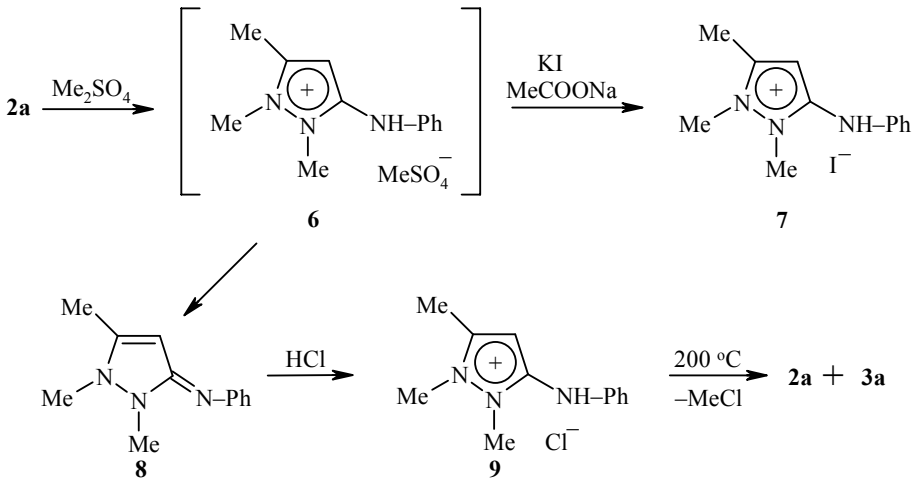
Bond	*d*, Å	Angle	ω, deg.
$N_{(1)}$–$N_{(2)}$	1.361(6)	$N_{(2)}$–$N_{(1)}$–$C_{(1)}$	104.7(4)
$N_{(1)}$–$C_{(1)}$	1.328(6)	$N_{(1)}$–$N_{(2)}$–$C_{(3)}$	112.0(4)
$N_{(2)}$–$C_{(3)}$	1.339(6)	$N_{(1)}$–$N_{(2)}$–$C_{(5)}$	120.1(4)
$N_{(2)}$–$C_{(5)}$	1.454(6)	$C_{(3)}$–$N_{(2)}$–$C_{(5)}$	127.8(4)
$N_{(3)}$–$C_{(3)}$	1.395(7)	$C_{(3)}$–$N_{(3)}$–$C_{(6)}$	120.5(5)
$N_{(3)}$–$C_{(6)}$	1.418(7)	$N_{(1)}$–$C_{(1)}$–$C_{(2)}$	111.1(4)
$C_{(1)}$–$C_{(2)}$	1.403(7)	$C_{(1)}$–$C_{(2)}$–$C_{(3)}$	105.0(4)
$C_{(1)}$–$C_{(4)}$	1.481(8)	$N_{(2)}$–$C_{(3)}$–$C_{(2)}$	107.1(4)
$C_{(2)}$–$C_{(3)}$	1.371(7)		

Since the 5-arylamino-1,3-dimethylpyrazoles **2a-c** are little studied we have carried out their chlorination (sulfuryl chloride in benzene) and bromination (a solution of bromine in acetic acid). When compared with the spectra of the starting compounds **2a-c**, the ^{1}H NMR spectra of the halogenation products (**4**, **5**) show the absence of the signal for the pyrazole ring proton (a singlet in the range 5.77-5.93 ppm).

In order to clear up the structure of the compound which, according to [7], is a result of the decomposition of the quaternary salt **9** we have carried out a series of reactions. The pyrazole **2a** was treated with dimethylsulfate to give the 5-anilino-1,2,3-trimethyl-1H-pyrazolium methylsulfate **6**.

Compound **6** was treated with a solution of sodium hydroxide to give the imine **8** which was then treated with gaseous HCl in dry ether to give the pyrazolium chloride **9**. The quaternary salt **9** was decomposed as reported in the method [7]. The melting point of the compound sythesized in this way was 94-95° which corresponded to the data in [7]. Using ^{1}H NMR spectroscopy it was shown that the result of the thermal decomposition of compound **9** is not the 1,3-dimethyl-5-phenylaminopyrazole **2a** as indicated in [7] but a mixture with the isomeric 1,5-dimethyl-3-phenylaminopyrazole **3a** in the approximate ratio 1:1.

This formation of an equal amount of the two isomeric pyrazoles **2a** and **3a** points to an approximately equal localization of the positive charge on both nitrogen atoms of the pyrazole ring in the pyrazolium chloride **9**.



The ^{1}H NMR spectrum of the 1,5-dimethyl-3-phenylaminopyrazole **3a** differs slightly from the ^{1}H NMR spectrum of 1,3-dimethyl-5-phenylaminopyrazole **2a** in that the signal of the pyrazole ring proton in compound **3a** is shifted by 0.17 ppm to high field and that of the NH group by 0.38 ppm to low field of the analogous proton signals in the isomeric compound **2a**. Evidently this is associated with the fact that , in the pyrazole **3a**, the two methyl groups situated in the 1 and 5 positions of the pyrazole ring slightly polarize the molecule of **3a** when compared with the isomeric pyrazole **2a**.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian-300 instrument (300 MHz) using TMS as internal standard.

4-Arylamino-4-thioxo-2-butanones were prepared as in method [8].

5-Arylamino-1,3-dimethylpyrazoles 2a-c. A solution of methylhydrazine (0.012 mol) in water (10 ml) was added to a solution of the 4-arylamino-4-thioxo-2-butanone **1** (0.01 mol) in acetic acid (40 ml) at 20°C and left for 24 h. The reaction product was diluted with cold water (100 ml) and filtered. A saturated solution of sodium acetate (50 ml) was added to the filtrate and left for 5 h at 4°C. The precipitated crystals of **2a-c** were filtered off, dried, and recrystallized from aqueous alcohol (1:1).

X-ray Structural Investigation of Compound 2a. Crystals of compound **2a** are monoclinic with $a = 11.187(7)$, $b = 7.826(4)$, $c = 11.876(9)$ Å; $\beta = 102.111(7)°$; $V = 1016.6$ Å^3; $Z = 4$; M = 187.25; $d = 1.22$ g/cm^3; space group $P2_1/c$; $\mu = 0.71$, $F(000) = 400$, crystal size 0.25 × 0.41 × 0.47 mm. Crystallographic measurements were carried out on an Enraf-Nonius CAD-4, four circle, automatic diffractometer at 18°C (MoKα radiation, $\lambda = 0.71069$ Å. relative scanning rate $\omega/2\theta = 1.2$, $2 < \theta < 25°$, spherical segment $0 < h < 12$, $0 < k < 8$, $-13 < l < 13$). In all, 1836 reflections were collected, of which 1597 were symmetrically independent with $R_{int} = 0.035$. The structure was solved by a direct method using least squares refinement in a full matrix, anisotropic approximation using the CRYSTALS [10] program package. 710 Reflections were used in the refinement with $I < 4\sigma I$ (131 refinement parameters, number of reflections per parameter 5.5). All of the hydrogen atoms were revealed in the electron density difference synthesis and included in the refinement with fixed positions and thermal parameters (only atom $H_{(3)}$, which takes part in the formation of an intramolecular bond, was refined isotropically). Calculation of the absorption in the crystal was carried out using the azimuthal scanning method [11]. In the refinement the Chebyshev weighting scheme [12] was used with five parameters: 0.85, -0.10, 0.60, -0.17, and 0.14. The final difference factor values were $R = 0.058$ and $R_w = 0.065$, $GOF = 1.207$. The residual electron density from the Fourier difference series 0.25 and -0.25 e/Å^3. Atomic coordinates are given in Table 2. The full set of crystallographic data has been deposited with the Cambridge structural data bank (register No CCDC 176864).

5-Arylamino-4-bromo-1,3-dimethylpyrazoles 4a-c. A solution of bromine (0.01 mol) in acetic acid (10 ml) was added to a solution of compound **2** (0.01 mol) in acetic acid (20 ml) at 20°C. After stirring for 4 h, the reaction product was diluted with a saturated solution of sodium acetate (40 ml). The precipitated product **4a-c** was filtered, dried, and recrystallized from ethanol.

5-Arylamino-1,3-dimethyl-4-chloropyrazoles 5a,b. A solution of sulfuryl chloride (0.01 mol) in benzene (10 ml) was added to a solution of compound **2a,b** (0.01 mol) in benzene (20 ml). After stirring for 6 h, the reaction product was washed with a solution of sodium acetate, dried over magnesium sulphate, and evaporated using a water pump vacuum. The Crystals of **5a,b** were recrystallized from ethanol.

3-Anilino-1,2,5-trimethyl-1H-pyrazolium iodide (7). A mixture of the pyrazole **2a** (0.01 mol) and dimethylsulfate (0.02 mol) was heated at 150°C for 10 min, cooled, water (5 ml) was added, and the product was heated until solution was complete. The reaction mixture was then treated with a saturated solution of aqueous KI. The precipitated solid **7** was filtered off, washed with ethanol (2 × 5 ml), and dried.

1,2,5-Trimethyl-3-phenylimino-2,3-dihydropyrazole (8). A mixture of the pyrazole **2a** (0.05 mol) and dimethylsulfate (0.1 mol) was heated at 150°C for 10 min, cooled, treated with a 20% solution of sodium hydroxide to a strongly basic reaction, and extracted with diethylether (2 × 20 ml). The combined ether extracts were dried over magnesium sulphate and the ether was evaporated off using a water pump vacuum. Standing at 4°C gave **8** as colorless crystals with a characteristic smell.

3-Anilino-1,2,5-trimethyl-1H-pyrazolium chloride (9). A current of dry hydrogen chloride was passed through a solution of compound **8** (0.01 mol) in ether (30 ml) at 20°C for 20 min. The reaction product **9** was separated as a rapidly solidifying oil. It was held for 2 h at 4°C, filtered, and washed with ether (2 × 10 ml).

Dehaloalkylation of compound 9. The chloride **9** (0.01 mol) was heated in a water pump vacuum at 200°C. Gases were evolved and the reaction products were sublimed and deposited on the cooled walls of a flask as a rapidly solidifying oil. Crystallization of the reaction product from hexane gave needles with mp 94-95°C. Fractional crystallization from hexane gave the 1,5-dimethyl-3-phenylaminopyrazole **3a**.

The authors thank the firm Aventis (Germany) for financial support of the investigation.

REFERENCES

1. D. R. Gupta and Sh. Naithani, *Acta Chim. Hung.*, **126**, 855 (1989).
2. R. G. Harrison, W. B. Jamieson, W. J. Ross, and J. C. Saunders, German Patent 2625227 (1975); *Chem. Abstr.*, **86**, 155658 (1977).
3. C. M. Passarotti, M. Valenti, and M. Grianti, *Curr. Toxicol. Ther.*, **1**, 89 (1993); *Chem. Abstr,*, **123**, 74469 (1995).
4. K. Nebel and H. G. Brunner, PCT Int. Appl. WO 96 01254 (1996); *Chem. Abstr.*, **124**, 289531 (1996).
5. M. Heil, N. Lui, V. Erdelen, U. Wachendorf-Neumann, and H. W. Dehne, German Patent 4405207 (1995); *Chem. Abstr.*, **124**, 8808 (1996).
6. O. Schallner, R. Gehring, E. Klauke, and J. Stetter, German Patent 3402308 (1984); *Chem. Abstr.*, **104**, 34075 (1986).
7. A. Mihaelis and A. Lachwitz, *Chem. Ber.*, **43**, 2114 (1910).
8. A. N. Borisevich and P. S. Pel'kis, *Khim. Geterotsikl. Soedin.*, 312 (1969).
9. L. J. Missio, H. S. Braibante, and M. E. F. Braibante, *J. Heterocycl. Chem.*, **33**, 1243 (1996).
10. D. J. Watkin, C. K. Prout, J. R. Carruthers, and P. W. Betteridge, CRYSTALS Issue 10. Chemical Crystallography Laboratory, Oxford University, Oxford (1996).
11. A. C. T. North, D. C. Phillips, and F. S. Mathews, *Acta Crystallogr.*, **A24**, 351 (1968).
12. J. R. Carruthers and D. J. Watkin, *Acta Crystallogr.*, **A35**, 698 (1979).